Remarks / Arguments

Claims 10-16 are pending in this application. Claims 1-9 have been cancelled.

Rejection under §103

Claims 10-16 stand rejected under §103 as being unpatentable over Haning (WO 98/40384, US 6,174,884) in view of Whalin and Egawa.

The examiner's argument would appear to be that

1) the Haning reference teaches a method of treating cerebrovascular diseases (e.g., stroke) comprising administering to a patient a PDE-II inhibitory compound of formula (I) as shown in present claim 10, such as the compound represented by example 39 Haning, which falls within formula (I),

2) the Whalin reference teaches that HL-725 (trequinsin), a potent inhibitor of isolated PDE II activity in vitor, can cause increased basal cAMP accumulation, potentiation of adenosine-stimulated cAMP accumulation, and retardation of the rate of cAMP decay,

3) the Egawa reference suggests that the therapeutic effect of a PDE IV inhibitor, rolipram, for learning and memory impairment is a result of the indirect potentiation of various transmitters by an increase in cAMP through the inhibition of PDE IV,

4) the motivation to employ the method of Haning in treating disorders of perception, learning, concentration, and perception resulting from stroke because these disorders are known to result from a stroke, and treating the underlying cause of these disorders would be expected to treat the listed disorders,

5) it is known that increasing cAMP results in amelioration of memory/learning impairment, leading to the conclusion that

6) one of ordinary skill in the art would be reasonably expected to employ any known potentiator of cAMP and enhancer for cAMP accumulation, including the compounds whose use is presently claimed, to treat memory and learning impairment regardless of the causative conditions.

For a rejection for obviousness to be proper, the art together with the knowledge of one skilled in the art, must suggest the claimed invention as a whole should be made, with an expectation of success. All claim limitations must be suggested. That standard is arguably not met here.

Haning discloses compounds which are stated to be useful for treatment of cardiovascular and cerebrovascular diseases, and states that these compounds inhibit either one of more of the c-GMP-metabolizing phosphodiesterases PDE I, PDE II and PDE V, leading to an increase in c-GMP. The reference states that the compounds can be used in medicaments for treating cardiovascular diseases, and provides a large list of exemplary cardiovascular diseases (including stroke). It also states that the compounds can be of importance for cerebral vascular diseases.

The Haning reference does not state that all the compounds it discloses are PDE II inhibitors. Rather, it states that the compounds inhibit one or more of PDE I, PDE II, and PDE V. Five compounds were tested for phosphodiesterase inhibition in vitro against PDE I, PDE II, and PDE V. Each of the tested compounds was shown to inhibit PDE II with an IC_{50} of between 100 and 500 nM. No test data were presented for other exemplary compounds. Thus, the reference only discloses that 5 tested compounds are PDE II inhibitors. The reference is silent with respect to the PDE II inhibitory activity of the remaining exemplary compounds.

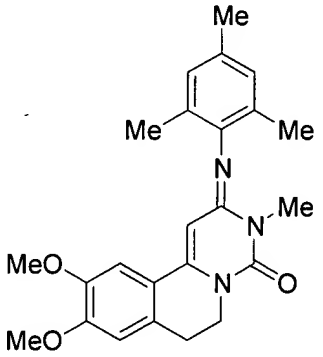
Haning does not disclose that <u>any</u> of his compounds are <u>selective</u> PDE 2 inhibitors as the term is defined in the present claims. Furthermore, although seven exemplary compounds of Haning (examples 18, 36, 39, 40, 49, 50, and 85) fall within the structural formula of present claim 10, none of these was tested by Haning and shown to be a PDE II inhibitor.

The Haning reference does state that the compounds there disclosed and claimed can be used in medicaments for treating a long list of cardiovascular diseases, one of which is stroke. However, there is no mention of the specific conditions identified in the present claim 10 (as the examiner recognized), and no suggestion that stroke should be selected from the list of conditions to be treated (as opposed to any of the other diseases listed), and no suggestion that the subset of compounds identified in present claim 10 (as opposed to any of the other compounds of the reference) should be employed for treatment of stroke.

It would seem that the only way for the examiner to select stroke would be to first view the disorders listed in present claim 10 and then make the connection to stroke, and the only way for the examiner to arrive at any compounds falling within the structural formula of present claim 10 would be first to understand the formula and then to determine whether any exemplary compounds of the reference fall within it. This constitutes hindsight reconstruction, and is improper.

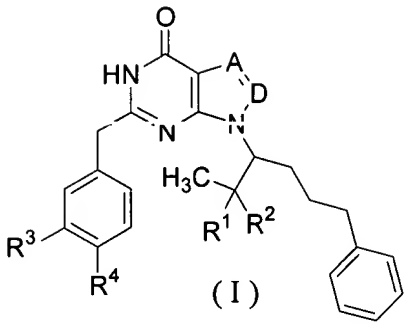
The examiner also cites the Whalin reference for its teachings relating to HL-725 (trequinsin) and quotes from the abstract, which states "Treatment of PC12 cells with HL-725 (a potent inhibitor of isolated PDE II activity *in vitro*) caused 1) increased basal cAMP accumulation, 2) potentiation of adenosine-stimulated cAMP accumulation, and 3) retardation of the rate of cAMP decay after removal of the adenosine stimulus. HL-725 blocked both the attenuation of cAMP accumulation and the accelerated rate of cAMP decay observed with the cGMP-elevating agents. These results suggest that, in PC12 cells, drugs or hormones that inhibit PDE II or increase intracellular cGMP levels to activate PDE II can modulate cAMP metabolism by altering the catalytic status of the enzyme."

Trequinsin (HL-725) has the chemical structure shown below.



Trequinsin
HL-725

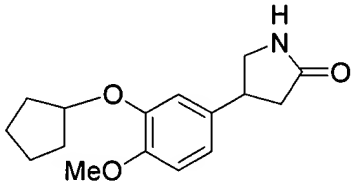
HL-75 is not similar to the compounds whose use is being claimed in the present application, the chemical structure of which is shown below. Accordingly, HL-725 cannot suggest using the selective PDE 2 inhibitors shown in present claim 10.



(I)

The examiner also cites the Egawa reference, stating that the reference suggests the therapeutic effects of a PDE IV inhibitor, rolipram, for learning and memory impairment results from the indirect potentiation of various transmitters by an increase in cAMP through the inhibition of PDE IV, and refers to the abstract. Actually, the last sentence of the abstract states, "These results suggest that the ameliorating effects of rolipram might result from the indirect potentiation of various transmitters including cholinergic and noradrenergic systems by an increase in cAMP with the inhibition of PDE4."

Rolipram is a PDE IV inhibitor having the chemical structure shown below.



Rolipram

This material is not similar to the compounds whose use is being claimed in the present application. Accordingly, rolipram cannot suggest using the selective PDE 2 inhibitors shown in claim 10.

In view of the above amendments and arguments, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,

William F. Gray

Reg. No.: 31018
Phone: (203) 812-2712
Date: 8 March 2004

William F. Gray
Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516-4175